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www.health.mo.gov/immunizations

webinar series

Barbara P. Yawn, MD MSc FAAFP

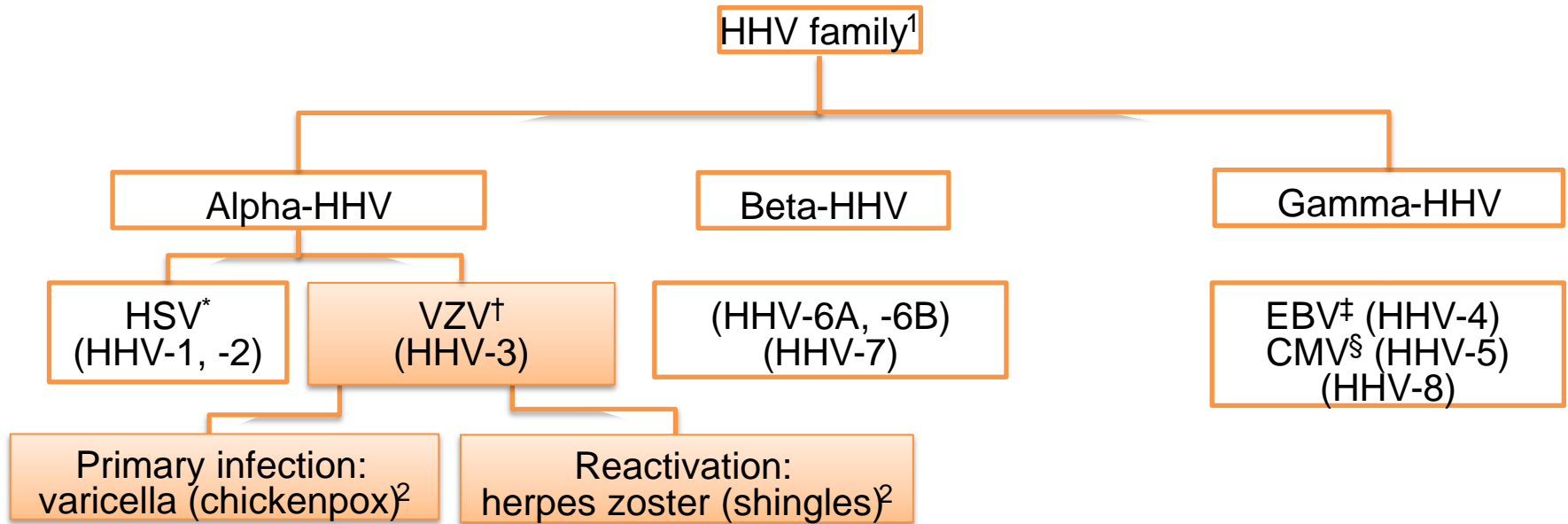
**Herpes Zoster: It's worse and better
than you thought.**

September 17, 2015

Objectives

- Review patho—physiology of herpes zoster (HZ)
- Review incidence and risk factors of HZ
- Review burden of HZ
- Review HZ recurrences
- Review prevention using HZ vaccine

Human Herpesviruses (HHV)



*HSV = herpes simplex virus

†VZV = varicella zoster virus

‡EBV = Epstein Barr virus

§CMV = cytomegalovirus

1. Roizman B, Pellett PE. In: Knipe DM, Howley PM, eds. *Fields Virology*. 4th ed. Vol 2. New York, NY: Lippincott Williams & Wilkins; 2001:2381-2397.

2. Arvin AM. In: Knipe DM, Howley PM, eds. *Fields Virology*. 4th ed. Vol 2. New York, NY: Lippincott Williams & Wilkins; 2001:2731-2767.

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HZ is common and burdensome

- 1 in every 3 people will develop HZ during their lifetime ¹
- People living to age 85 years, have a 1 in 2 chance of developing HZ
- Both the incidence and the complication rates of HZ increase with age ¹
- HZ causes a significant burden for affected individuals

1. Harpaz R Ortega-Sanchez IR Seward JF Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep (2008 Jun 6) 57(RR-5):1-30; quiz CE2-4

Diagnosis of Zoster

- Clinical findings
 - Distinctive unilateral, vesicular rash allows accurate diagnosis in the majority of cases.¹
 - In immunocompromised patients, zoster may be more severe, with cutaneous dissemination.²
- Laboratory confirmation—but only so/so
 - Tzanck smear³
 - Viral culture³
 - Direct immunofluorescence assay³
 - Polymerase-chain reaction³

1. Gnann JW, Whitley RJ. N Engl J Med. 2002;247:340-346.

2. Oxman MN. In: Arvin AM, Gershon AA, eds. Varicella-Zoster Virus: Virology and Clinical Management. Cambridge, UK: Cambridge University Press; 2000:246-275.

3. Straus SE, Oxman MN. In: Freedberg IM, Eisen AZ, Wolff K, et al, eds. Fitzpatrick's Dermatology in General Medicine. 5th ed. Vol 2. New York, NY: McGraw-Hill; 1999:2427-2450.

Zoster: Clinical Features

- Usually limited to 1 or 2 adjacent, unilateral dermatomes.¹
- “Grapelike” lesions clustered on an erythematous base.²
- Lesions usually heal within 4 weeks.¹



Courtesy of the American College of Physicians
(www.acponline.org/shell-cgi/printhappy.pl/bioterro/smallpox_mimics.htm).

1. Oxman MN. In: Arvin AM, Gershon AA, eds. *Varicella-Zoster Virus: Virology and Clinical Management*. Cambridge, UK: Cambridge University Press; 2000:246–275. 2. Lycka BAS, Williamson D, Sibbald RG. *Herpes Zoster and Postherpetic Neuralgia, 2nd Revised and Enlarged Edition*. Vol 11. Amsterdam, The Netherlands: Elsevier Science B.V.; 2001:97–106.

Zoster: Latency and Reactivation

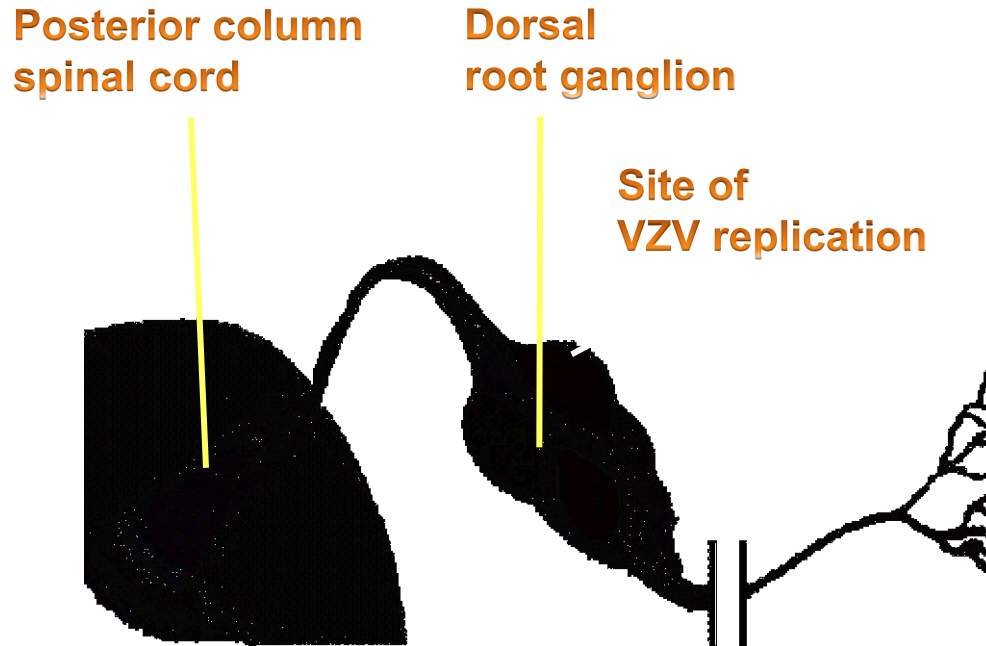
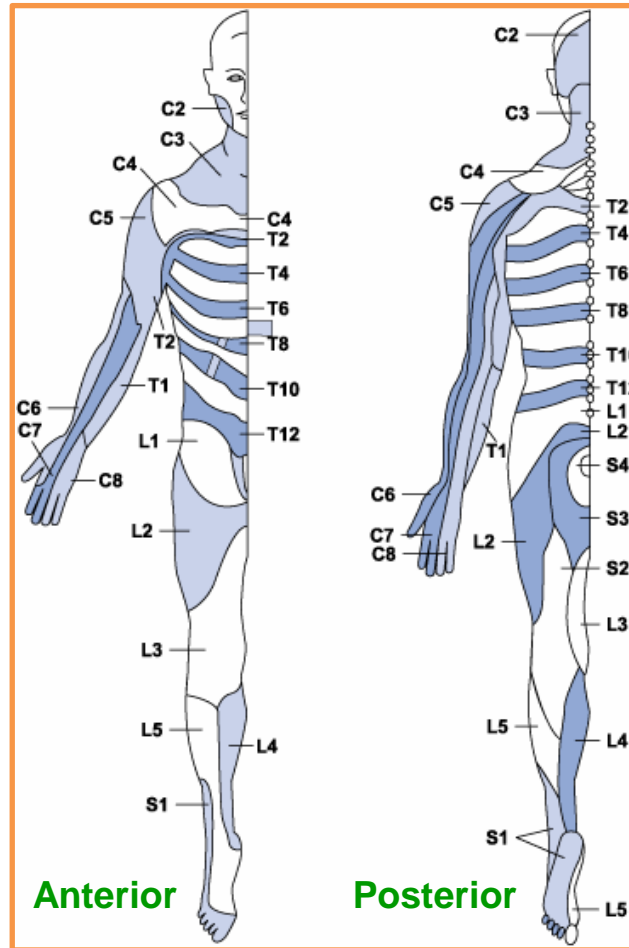


Image courtesy of Thomas P. Habif, MD.

Zoster: Dermatomal Distribution



© Phototake. Reprinted with permission.



From Asbury AK. © 2001. Reprinted with permission of McGrawHill.¹

Asbury AK, et al. © 2001. Adapted with permission of McGrawHill.¹

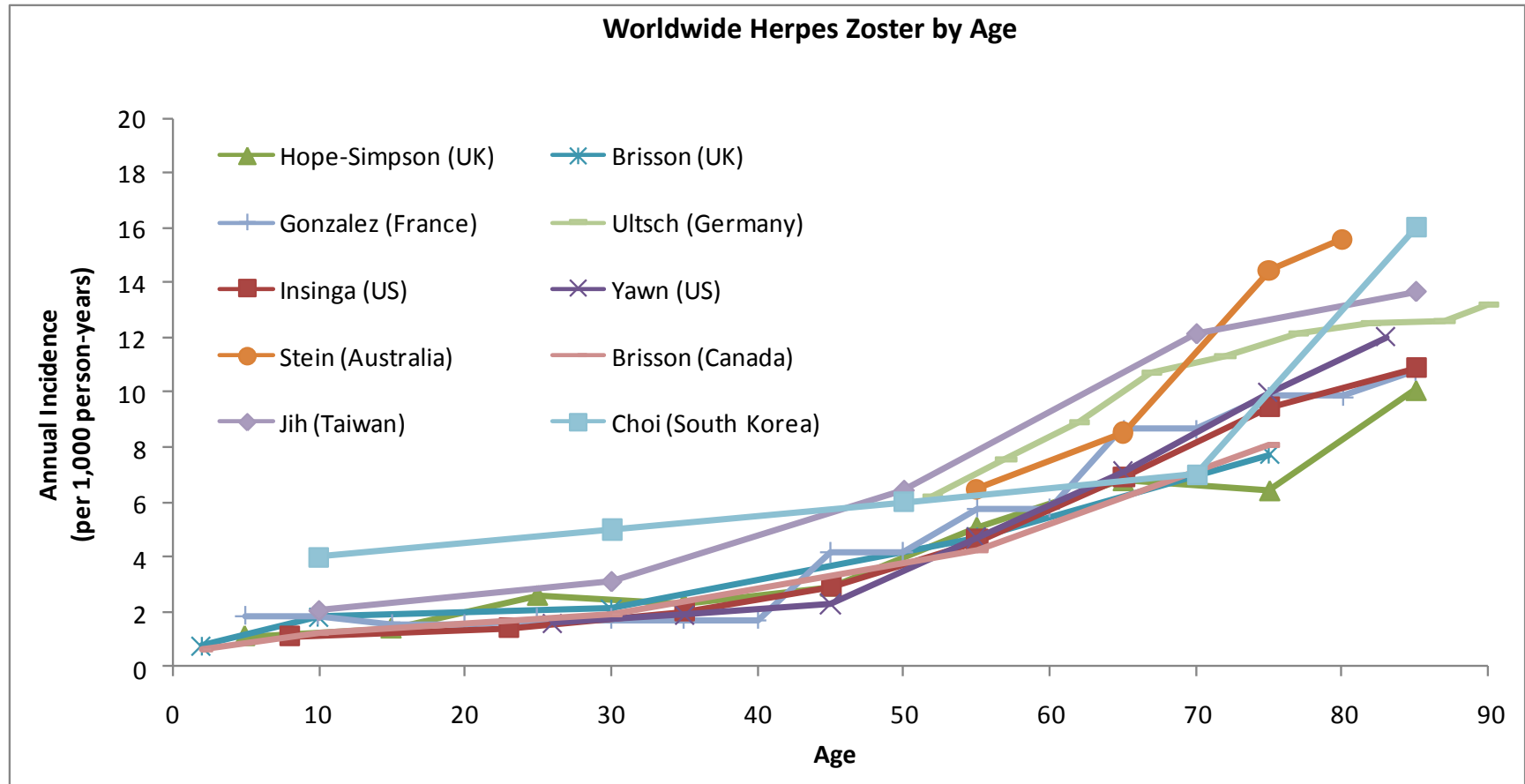
1. Asbury AK. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Logo DL, Jameson JL, eds. *Harrison's Principles of Internal Medicine* 15th ed. New York, NY: McGrawHill; 2001:128-132.

VZV: Immune Response

- Cell-mediated immunity (CMI) plays a major role.¹
 - Clears virally infected cells
 - Limits viral replication at dermal sites
- Humoral immunity²
 - IgM, IgG, IgA are neutralizing antibodies.
- Immunity persists following disease.
 - Waning CMI with increasing age may contribute to reactivation of VZV as herpes zoster (shingles).³

1. Arvin AM. In: Knipe DM, Howley PM, eds. Fields Virology. 4th ed. Vol 2. Lippincott Williams & Wilkins; 2001:2731–2767.
2. Abendroth A, Arvin AM. In: Arvin AM, Gershon AA, eds. Varicella-Zoster Virus. Virology and Clinical Management. Cambridge University Press; 2000:142–156.
3. Straus SE, Oxman MN. In: Freedberg IM, Eisen AZ, Wolff K, et al, eds. Fitzpatrick's Dermatology in General Medicine. 5th ed. Vol 2. McGraw-Hill; 1999:2427–2450.

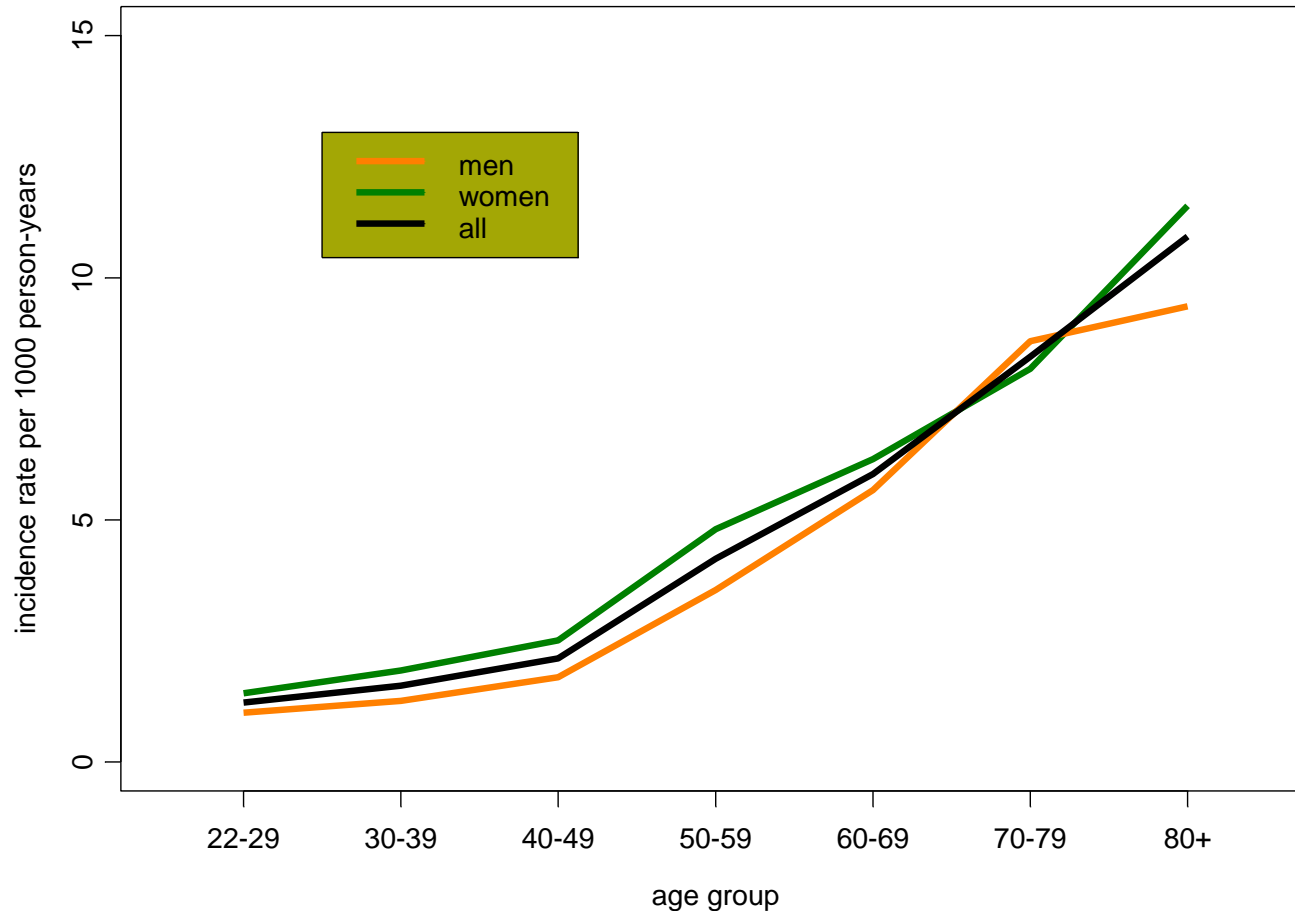
Herpes Zoster by Worldwide Age¹⁻⁹



Brisson M et al. *Epidemiol Infect.* 2001;127:305–314.
 Choi WS et al. *J Clin Virol.* 2010;47:325–329.
 Gonzalez Chiappe S et al. *Vaccine.* 2010;28:7933–7938.
 Hope-Simpson RE. *Proc R Soc Med.* 1965;58:9–20.
 Insinga RP et al. *J Gen Intern Med.* 2005;20:748–753.

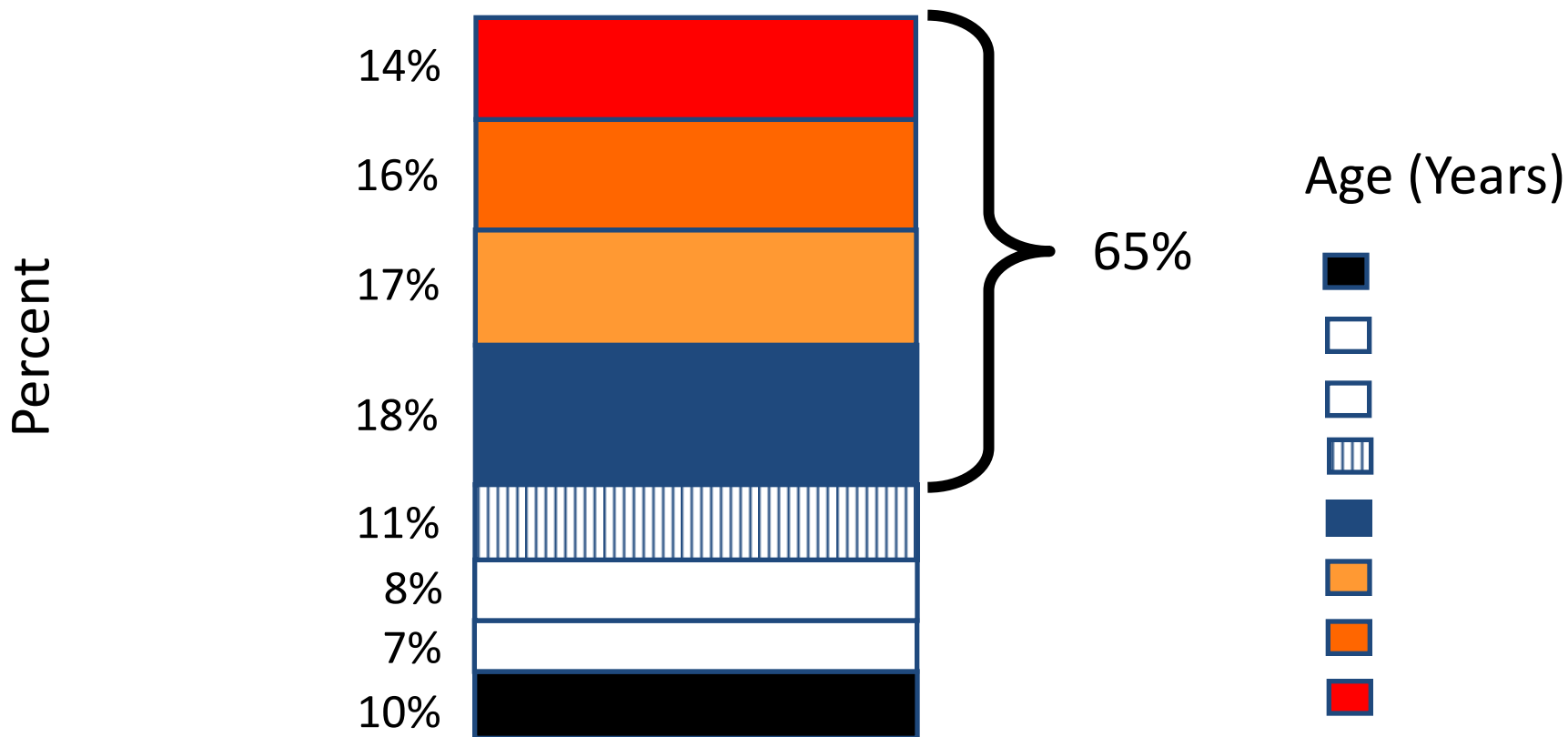
Jih JS et al. *Acta Derm Venereol.* 2009;89:612–616.
 Stein AN et al. *Vaccine.* 2009;27:520–529.
 Ultsch B et al. *BMC Infect Dis.* 2011;11:173.
 Yawn BP et al. *Mayo Clin Proc.* 2007;82:1341–1349
 Araujo LQ et al. *Herpes* 2007 14 (supplement 2) 40A-44A.

HZ Incidence by age group and sex



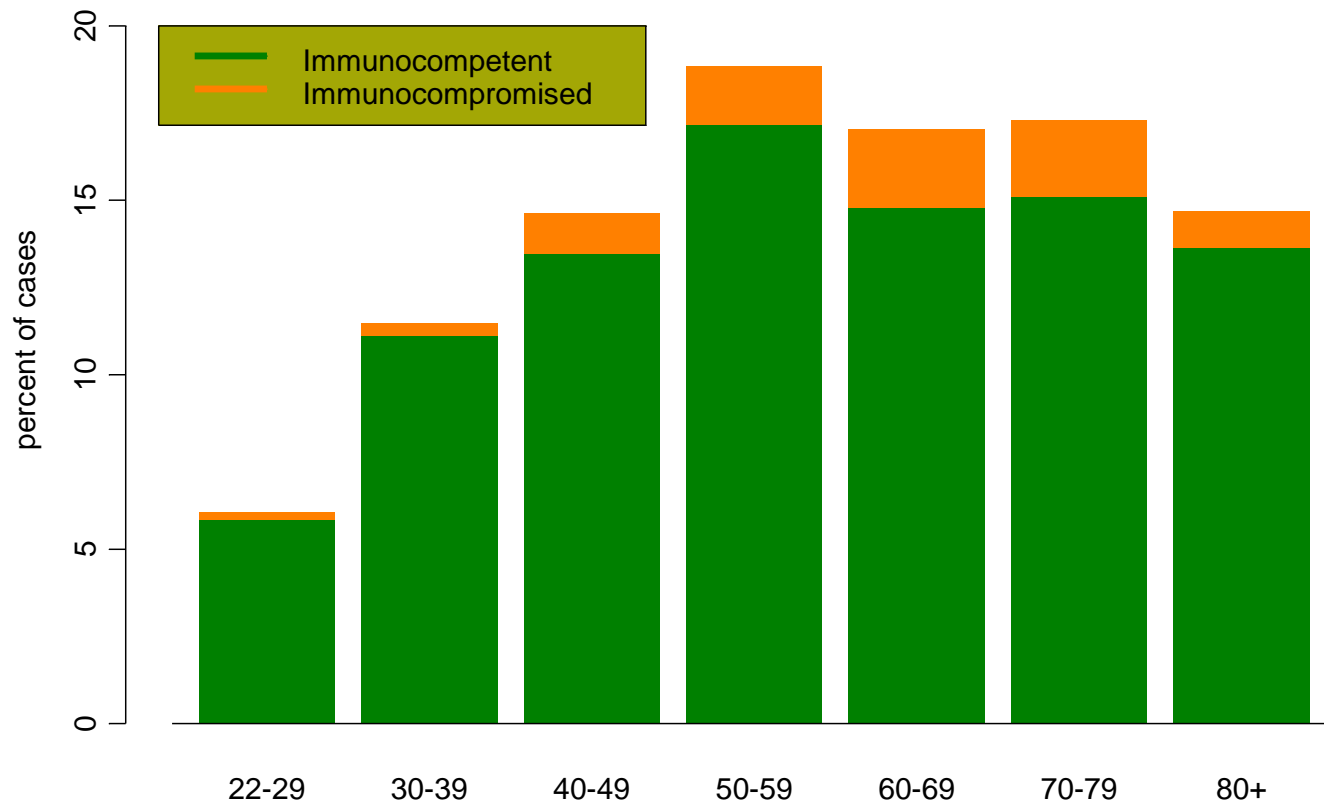
Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. Mayo Clin Proc. 2007;82(11):1341-9

Distribution of HZ Cases by Age



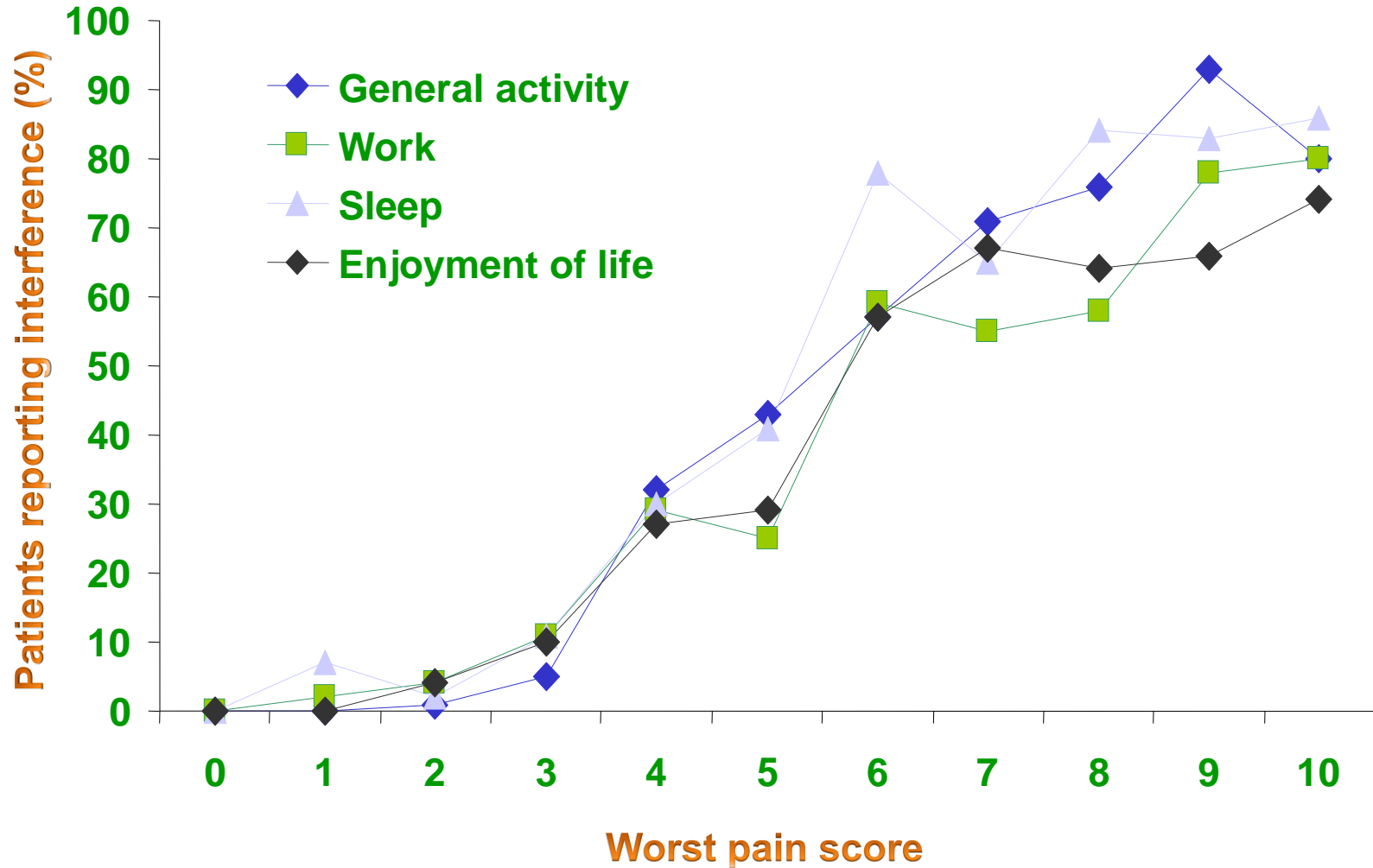
❖ Preliminary data from Olmsted County, 2005.
The number of HZ cases was calculated by applying the Olmsted HZ incidence rates to the 2005 US population.

Distribution of HZ cases by age and immune status



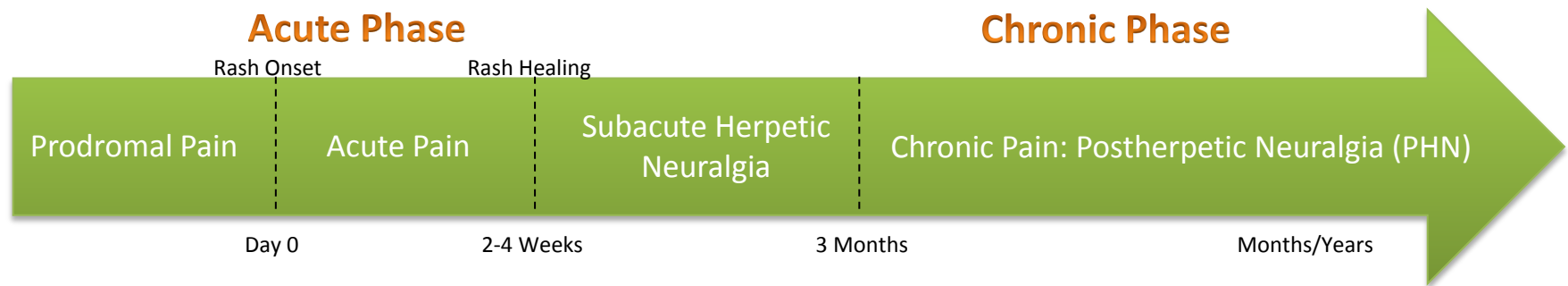
Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS. *A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction.* Mayo Clin Proc. 2007;82(11):1341-9.

Effect of Zoster on Activities of Daily Living



Adapted from Lydick E, Epstein RS, Himmelberger D, White CJ. *Neurology*. 1995;45(suppl 8):S52-S53.

HZ Associated Pain



- Prodromal pain mimics other conditions.
- Acute pain=lost work, play, sleep and prescription Rx
- PHN is a chronic neuropathic pain syndrome
- PHN can persist for months or years¹
- PHN occurs in 8%-30% of herpes zoster cases²⁻¹⁵
 - 34%-73% in those over 70 yo^{2,4,6,8,10,12,13}

1. Johnson RW, Bouhassira D, Kassianos G, et al *BMC Medicine* 2010;8:37. 2. Arvin AM. *Clin Microbio Reviews*. 1996;9:361–381. 3. Johnson RW, Whitton TL. *Expert Op on Pharmacotherapy*. 2004;5:551–559. 4. Gross G, Schöfer H, Wassilew S, et al. *J of Clin Vir*. 2003;26:277–289. 5. Schmader KE. *Clin J Pain*. 2002;18:350–354. 6. Edmunds WJ, Brisson M, Rose JD. *Vac*. 2001;19:3076–3090. 7. Bowsher D. *Euro J of Pain*. 1999;3:335–342. 8. Arvin A. Varicella-zoster virus. Knipe DM, Howley PM, eds. *Fields Virology* 2001:2731–2767. 9. Rusthoven JJ. *Transfus Med Rev*. 1994;8:96–116. 10. Chidiac C, Bruxelle J, Daures JP, et al. *Clin Infect Dis*. 2001;33:62–69. 11. Coen PG, Scott F, Leedham-Green M, et al. *Eur J Pain*. 2006;10:695–700. 12. Scott FT, Leedham-Green ME, Barrett-Muir WY, et al. *J Med Virol*. 2003;70 Suppl 1:S24–30. 13. Mamdani FS. *Can Fam Physician*. 1994;40:321–326, 329–332. 14. Baron R. *Eur J Neurol*. 2004;11 Suppl 1:3–11. 15. Richards P. *Arch Fam Med*. 1996;5:42–46. 15. Yawn BP, et al *Mayo Clin Proc* 2007;8(2);1341-9

Health Care Use for HZ

- 30% of people with HZ make a visit for prodromal
- On average 3 ambulatory visits per HZ case
- 4% of HZ cases hospitalized
- > 70% of HZ cases receive antivirals
- Broad use of opiates, but also of antidepressants , anticonvulsants
 - HZ-related pain resistant to treatment
- Health care use due to HZ increases with age

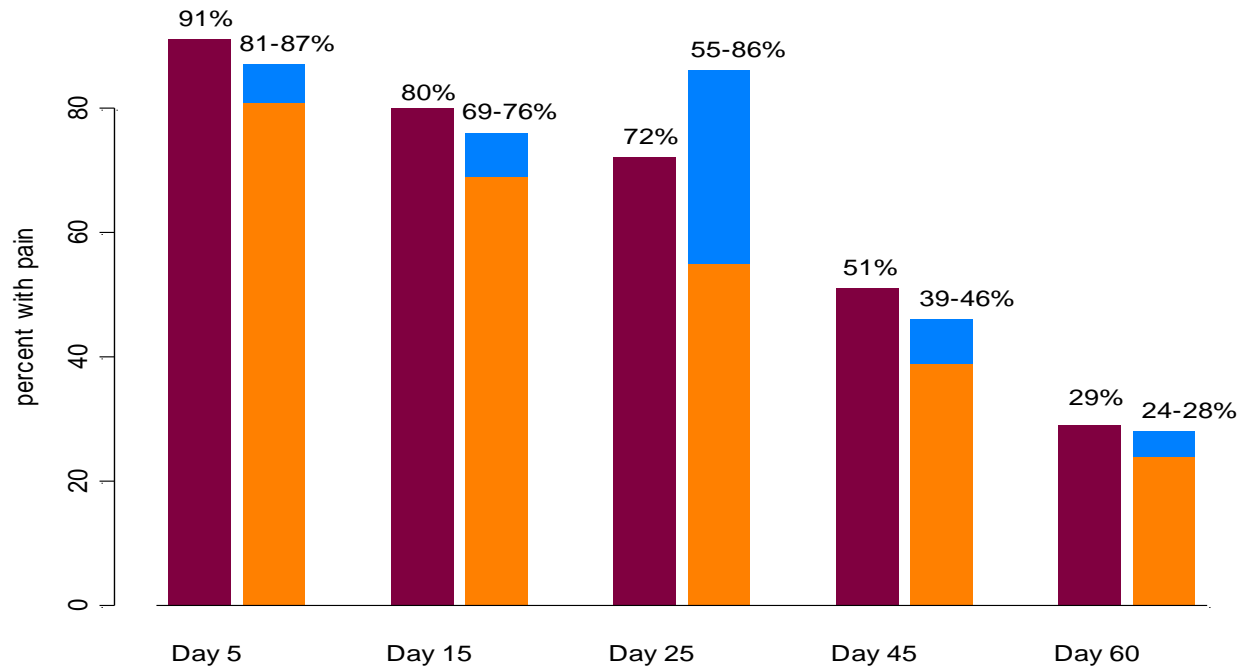
Prodromal Phase of Zoster

- Pain and paresthesia may precede the vesicular rash.¹
 - Sensations range from itching to severe lancinating pain.^{1,2}
 - 40% of patients experience pain >4 days before eruption.²
 - Prodrome common in persons >60 years of age.¹
 - Pain may mimic other conditions^{1,3}
- Constitutional symptoms²
 - Headache, malaise, fever

1. Oxman MN. In: Arvin AM, Gershon AA, eds. Varicella-Zoster Virus: Virology and Clinical Management. Cambridge, UK: Cambridge University Press: 2000:246-275.
2. Lycka BAS, Williamson D, Sibbald RG. Herpes Zoster and Postherpetic Neuralgia, 2nd Revised and Enlarged Edition. Vol 11. Amsterdam, The Netherlands: Elsevier Science B.V.: 2001:97-106.
3. Straus SE, Oxman MN. In: Freedberg IM, Eisen AZ, Wolffk, et al, eds. Fitzpatrick's Dermatology in General Medicine. 5th ed. Vol 2. New York, NY: McGraw-Hill; 1999:427-2450. 4. Gnann JW, Whitley RJ. N Engl J Med. 2002;247:340-346.

Therapy for acute HZ

Anti-viral therapy—little reduction in pain



Therapy for acute HZ

Pain Medications:

OTC---modest effect

Opioids---side effects

constipation

loss of balance--falls

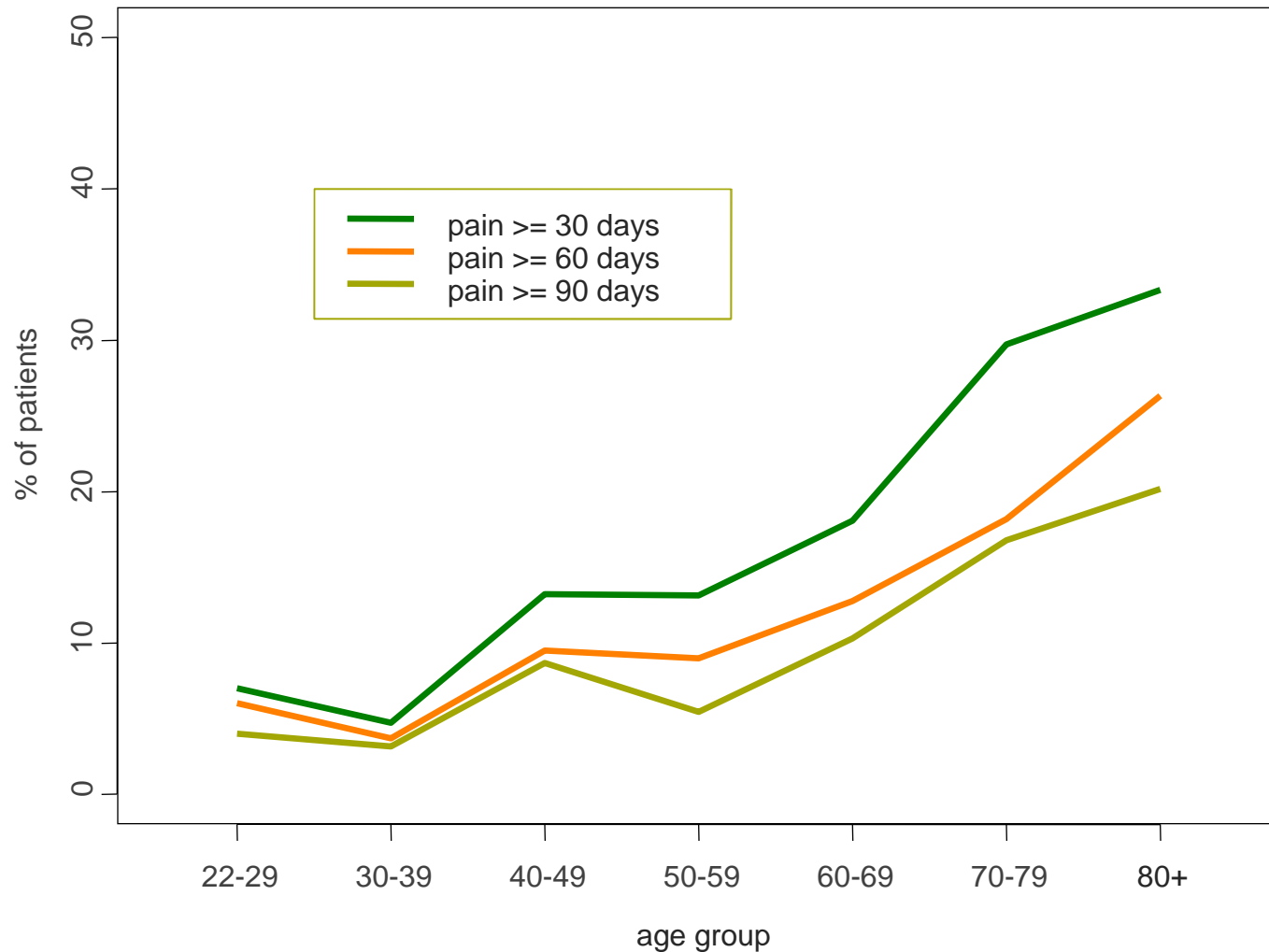
patient concerns

Antidepressants

Neuroleptics

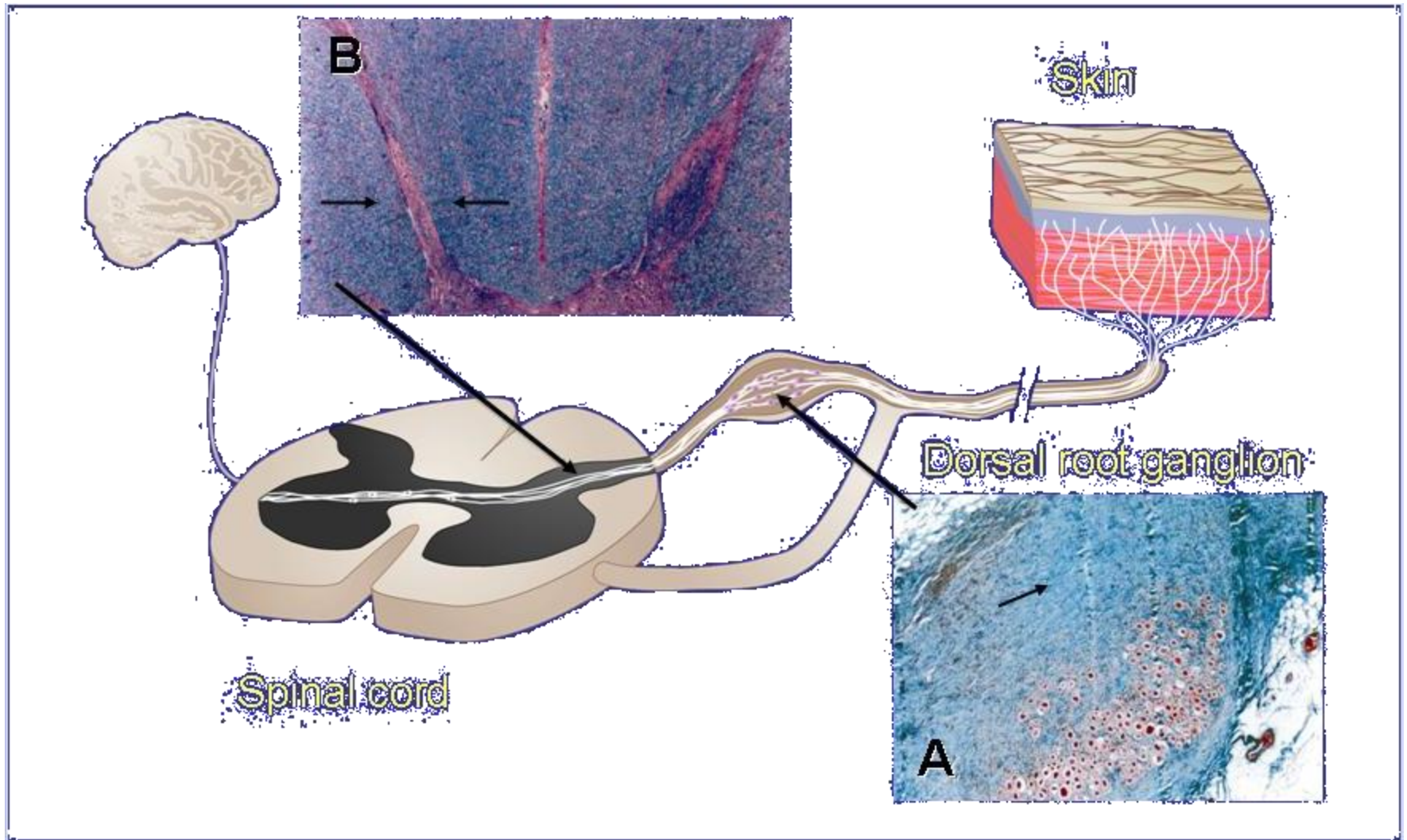
Often too little, too late

Pain duration >90 days by age group



1. Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. *Mayo Clin Proc.* 2007;82(11):1341-9.
2. Drolet M, Brisson M, Schmader K, Levin M, Johnson R, Oxman M, Patrick D, Camden S, Mansi JA. Predictors of Postherpetic Neuralgia Among Patients with Herpes Zoster: A Prospective Study. *J Pain.* Nov 2007; 11(11):1211-21.

Pathophysiology of PHN



A,B: Reprinted from Herpes Zoster and Postherpetic Neuralgia, 2nd Revised and Enlarged Edition. Vol 11. Watson CPN, Oaklander AL, Deck JH, The neuropathy of herpes zoster with particular reference to postherpetic neuralgia and its pathogenesis, pp167-182, 2001, with permission from Elsevier

Postherpetic Neuralgia (PHN)

- PHN is a chronic neuropathic pain syndrome that persists or recurs in the dermatome affected by Zoster.¹
- Definitions of PHN vary, and have included²
 - Any pain persisting after healing of zoster lesions
 - Pain persisting 1 month after rash onset
 - Pain persisting 3 months after rash onset

Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS. *A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction*. Mayo Clin Proc. 2007;82(11):1341-9. **2.** Drolet M, Brisson M, Schmader K, Levin M, Johnson R, Oxman M, Patrick D, Camden S, Mansi JA. *Predictors of Postherpetic Neuralgia Among Patients with Herpes Zoster: A Prospective Study*. J Pain. Nov 2007; 11(11):1211-21.

Therapy for PHN

- Pain medication
- Antidepressants
- Neuroleptics
- TENS
- Injections
- Often limited relief and many adverse effects

Spectrum of Sensory Abnormalities in PHN

- Spontaneous pain¹
 - Continuous or paroxysmal
 - Burning, stabbing, shooting
- Stimulus-evoked pain²
- Partial sensory deficit¹
- Parasthesias/dysesthesias²
- Autonomic instability may occur¹
 - - Signs include sweating, erythema

1. Bowsher D. In: Watson CPN, Gershon AA, eds. Herpes Zoster and Postherpetic Neuralgia. 2nd Revised and Enlarged Edition. Vol 11. Amsterdam, The Netherlands: Elsevier Science B.V.; 2001;143-147.
2. Dworkin RH. Clin J Pain. 2002;18:343-349.

Risk Factors for PHN¹

- Older age
- More severe acute zoster pain
- Greater rash severity
- Greater sensory abnormalities during acute zoster
- Prodrome prior to zoster rash

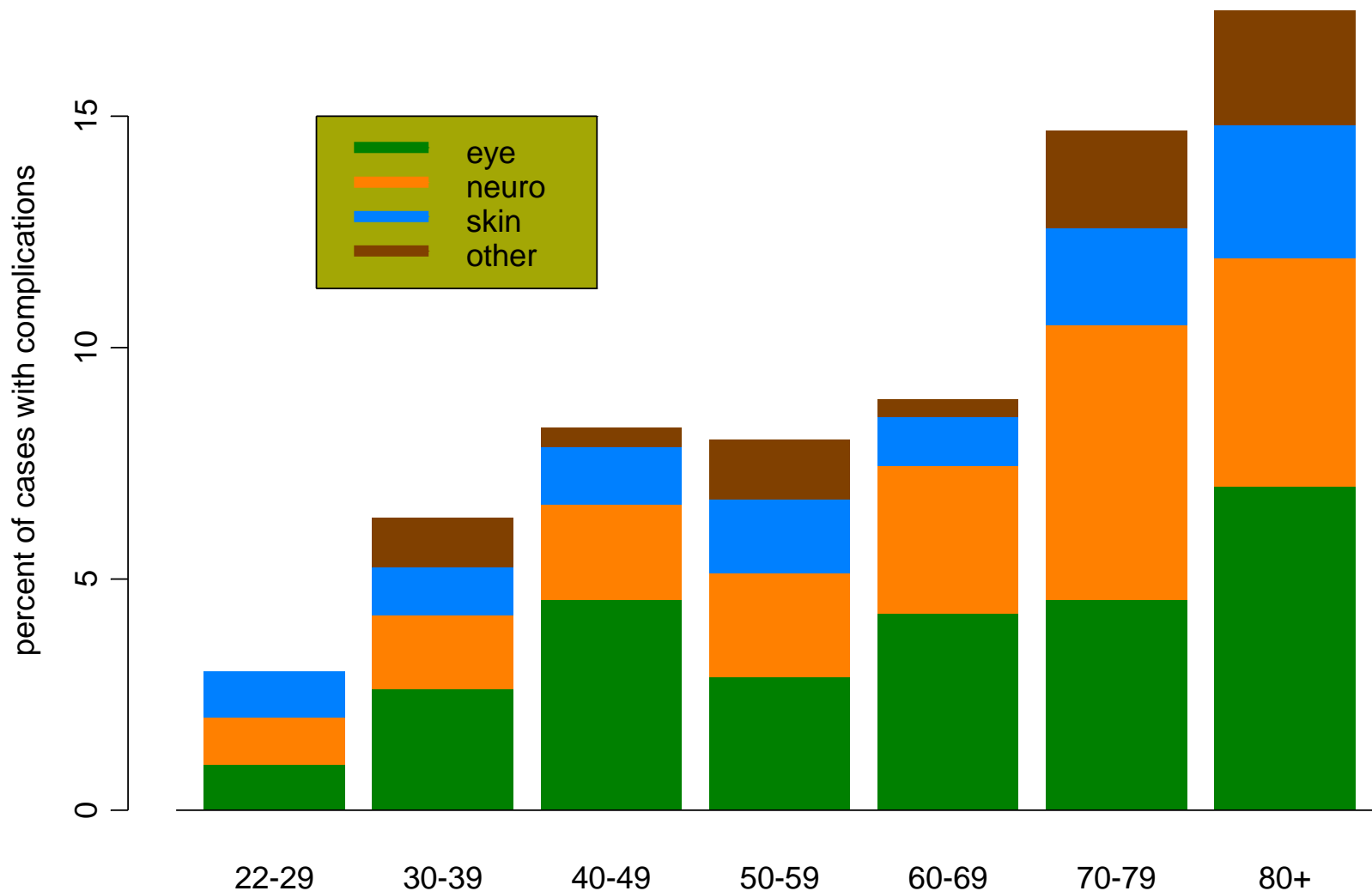
Dworkin RH, Schmader KE. In: Watson CPN, Gershon AA, eds. Herpes Zoster and Postherpetic Neuralgia. 2nd Revised and Enlarged Edition. Vol 11. Amsterdam, The Netherlands: Elsevier Science B.V.; 2001:39-64.

Impact of PHN

- Clinical observations include¹:
 - Depression and other psychological distress
 - Physical, occupational, and social impairments resulting from constant pain

1. Schmader K. Vaccine. 1998;16:1768-1770.

Non-pain Complication rates by age

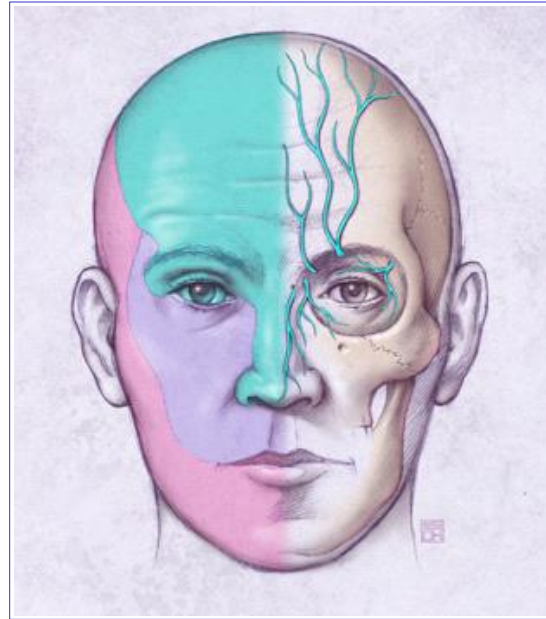


Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. Mayo Clin Proc. 2007;82(11):1341-9.

Zoster Ophthalmicus



Image courtesy of Charles E. Crutchfield III, MD. Crutchfield Dermatology, Eagan, MN.

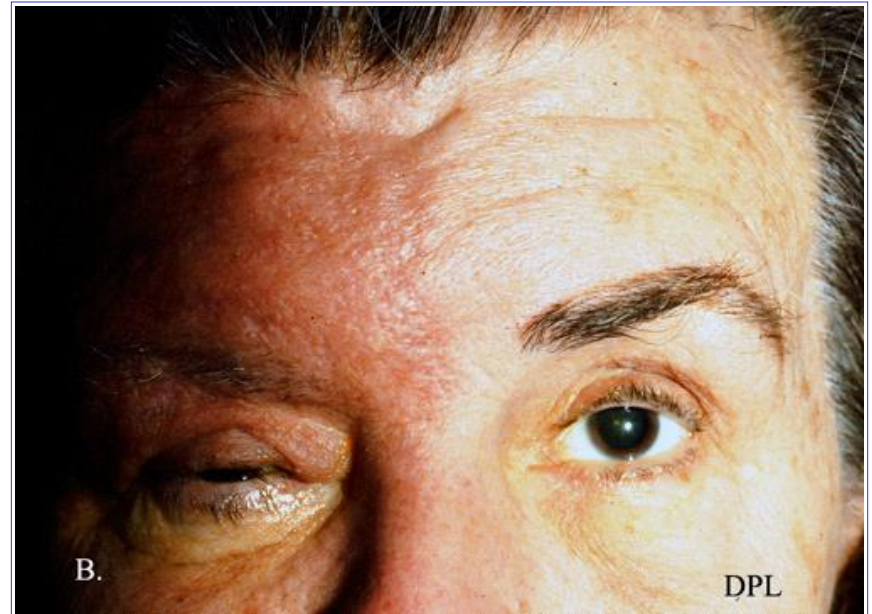


KO Studios, Pacifica, CA.
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Image courtesy of
Dr. Dubin's collection (www.skinatlas.com).

Scarring: Ophthalmic Zoster



From Pavan-Langston D. Ophthalmic zoster. In: Arvin AM, Gershon AA, eds. *Varicella-Zoster Virus: Virology and Clinical Management*. Cambridge, UK: Cambridge University Press; 2000:276–298. Reproduced with the permission of Cambridge University Press.

Recurrences

- 1669 HZ cases: mean follow up 7.3 years
- 105 HZ recurrences in 95 individuals
 - 7 people had 2 recurrences and 1 had 4 (IC)
- The recurrence rates at 8 years were:
 - 7.2% (95% CI, 5.4-9.0) for women
 - 4.5% (95% CI, 2.8-6.2) for men
- 55% of the recurrences in the same site
- HZ recurrences noted 3 months to 10 years later

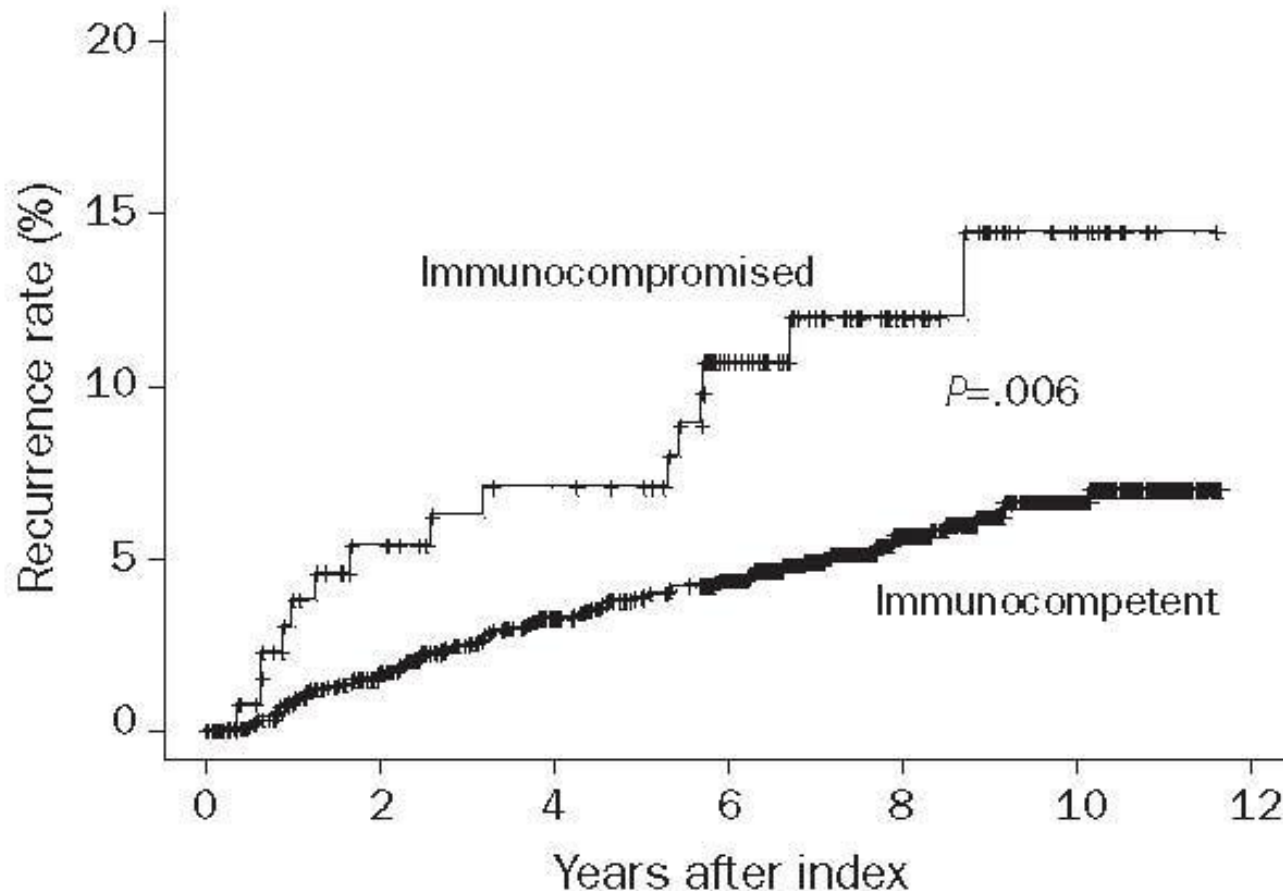
1. Hope-Simpson 1965.
2. Epstein 1980.
3. Donahue 1995.
4. Oxman 2005.
5. Yawn BP, Wollan PC, Kurland MJ, St Sauver JL, Saddier P. *Herpes Zoster Recurrences More Frequent than Previously Reported*. Mayo Clinic Proceedings; Feb 2011 :86(2):88-93.

Risk factors for HZ recurrence

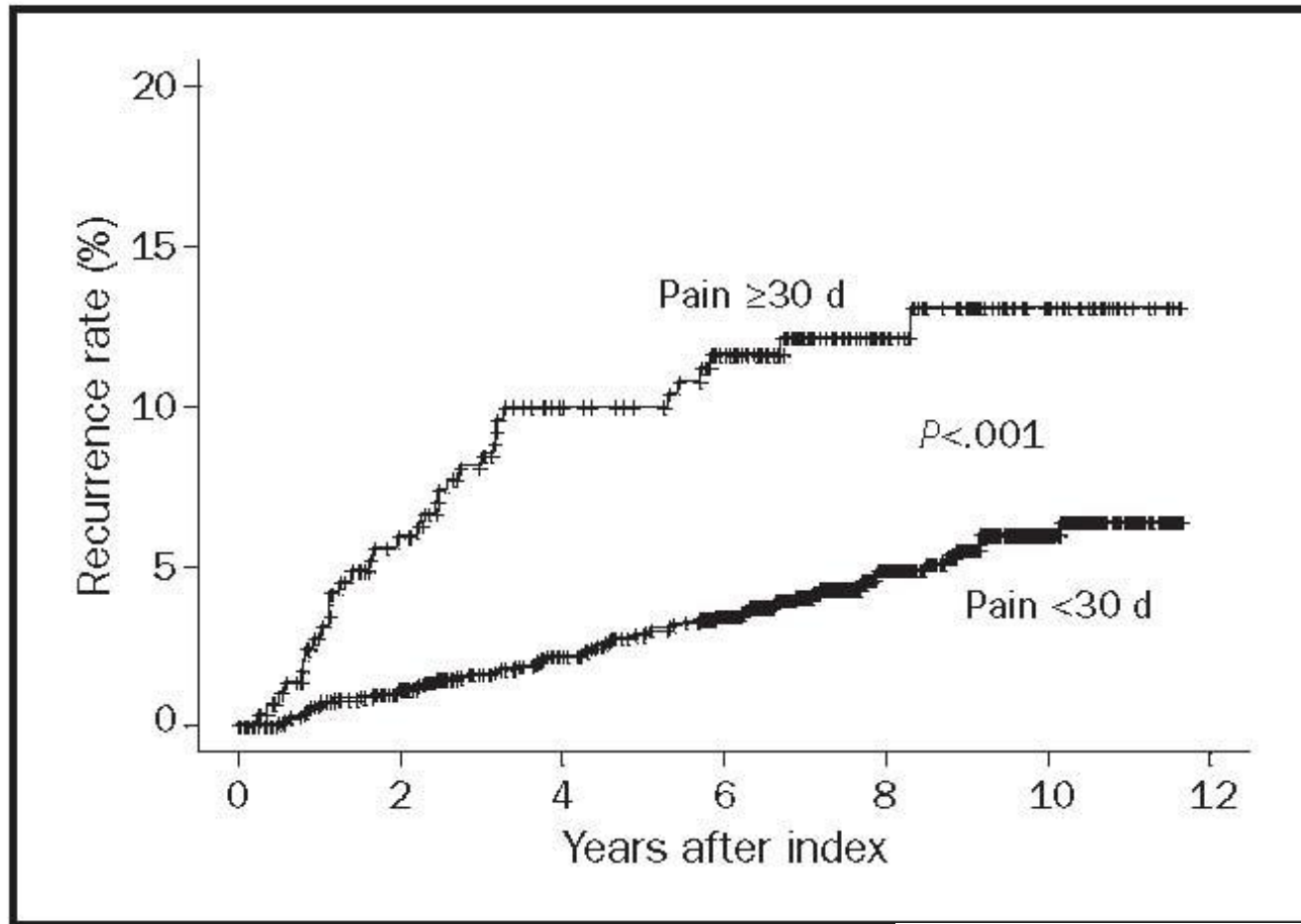
Factor	Multivariate Cox Regression Hazard ratio (95% CI) p-value
Age <50	0.42 (0.2, 0.8) p = 0.006
Sex (female)	1.45 (0.4, 1.1) p = 0.10
Immune-compromised	1.64 (0.9, 2.9) p = 0.09
Pain duration 30 days or more in the initial episode.	1.57 (0.9, 2.6) p = 0.08
Age>50 and Pain>=30 days (interaction)	5.81 (2.3,15.0) p = .0003

Yawn BP, Wollan PC, Kurland MJ, St Sauver JL, Saddier P. *Herpes Zoster Recurrences More Frequent than Previously Reported*. Mayo Clinic Proceedings; Feb 2011 :86(2):88-93.

HZ Recurrence Rate by Immune Status



HZ Recurrence Rate by Pain Status



Yawn BP, et al. Mayo Clin Proc. 2011;86(2):88-93.

Clinical Summary:

HZ is common and has a large disease burden

- 1 in 3 adults by age 80

- Acute pain as well as PHN, eye and other issues

- 30% of people visit MD before the rash

- Recurrence rates similar to occurrence rates

Complications can last days to a life time

Prevention is possible

- Better at younger ages---start vaccine at 50

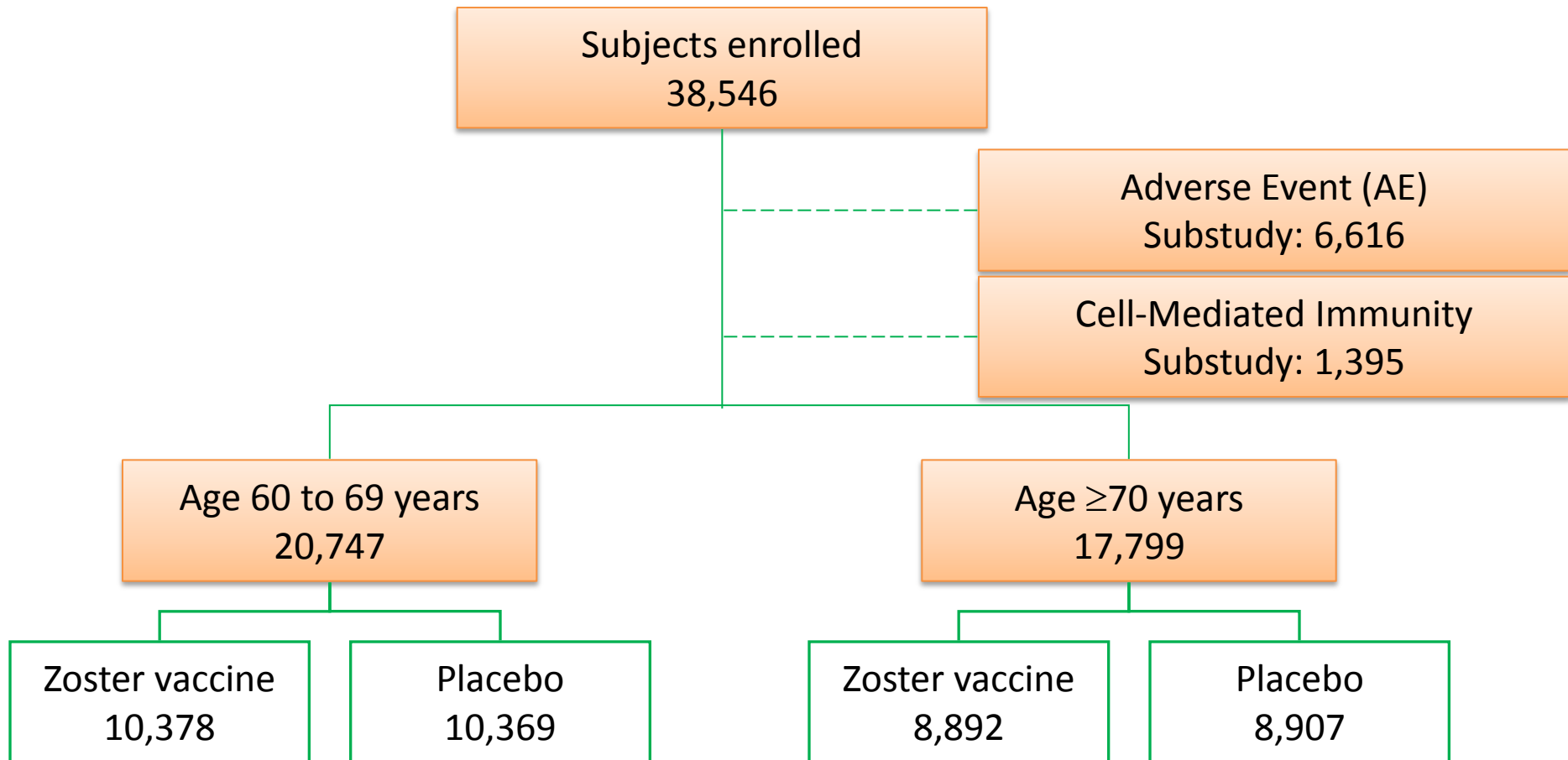
Decrease in risk of PHN goes beyond HZ prevention

- Breakthrough cases have less PHN

Zostavax for prevention:

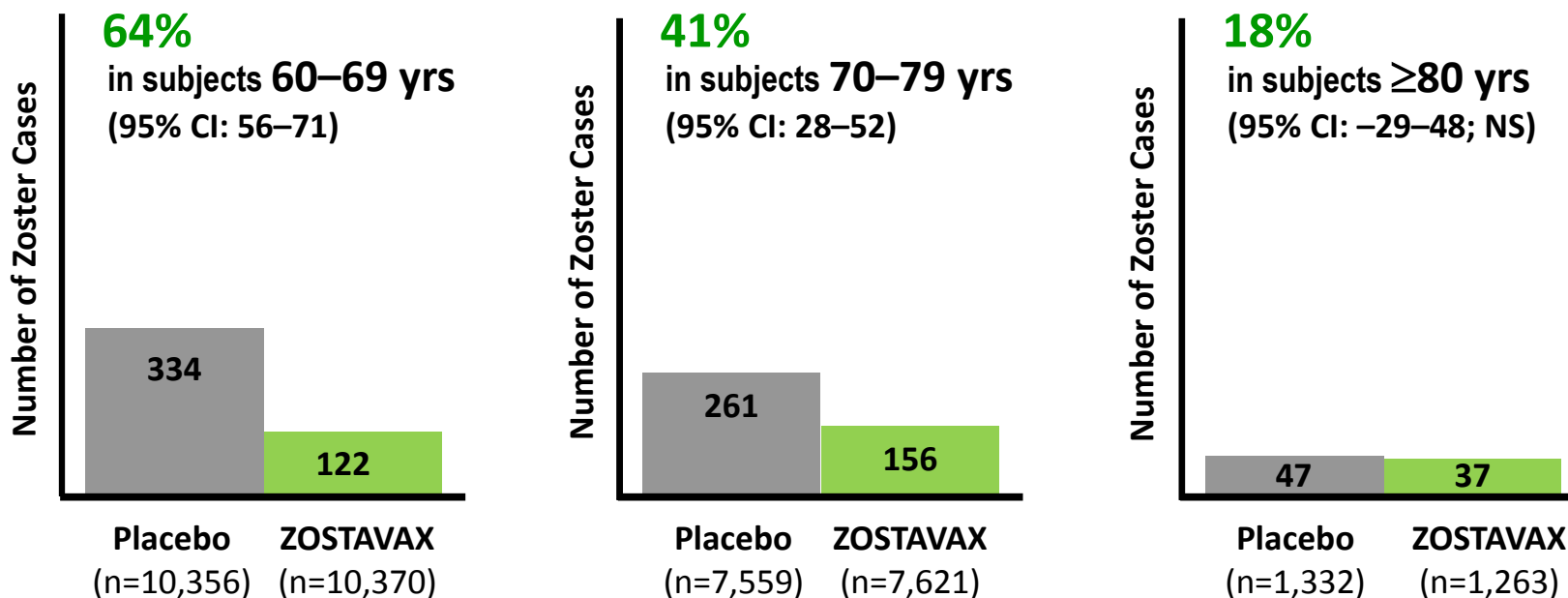
- Live attenuated
- Lypolized—frozen
- Must be reconstituted
- Short useable period after mixing
- Approved for use in non-immune compromised age 50 and older
- Single dose

Randomization of Subjects in the Shingles Prevention Study (SPS)

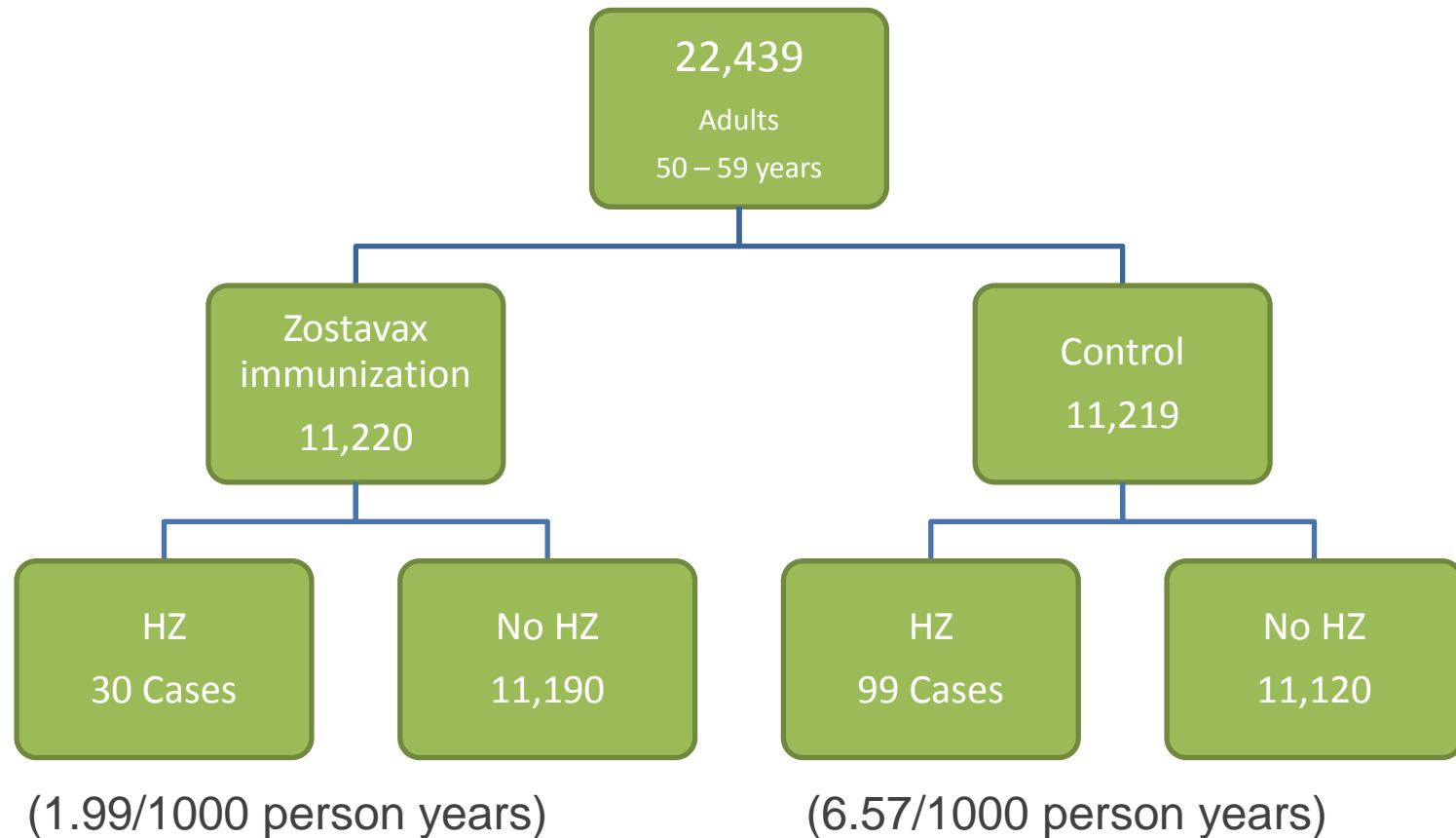


SPS: Efficacy of ZOSTAVAX® on Herpes Zoster Incidence Compared With Placebo by Age Group

- Vaccine efficacy for the prevention of herpes zoster was highest in those subjects 60 to 69 years of age and declined with increasing age.



ZEST: Overall Efficacy of ZOSTAVAX® on Herpes Zoster Incidence Compared With Placebo

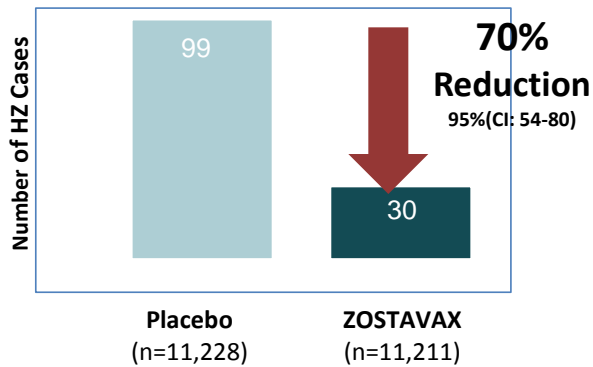


Efficacy 69.8% (54.1-80.6)

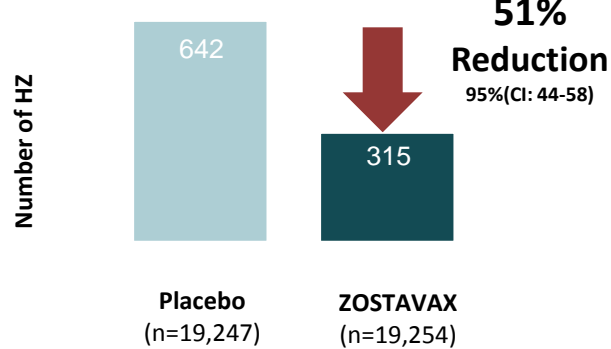
Summary: ZOSTAVAX® is Highly Effective in Reducing the Incidence of Herpes Zoster and positive effects to Postherpetic Neuralgia

* ZOSTAVAX is not indicated for prevention of PHN

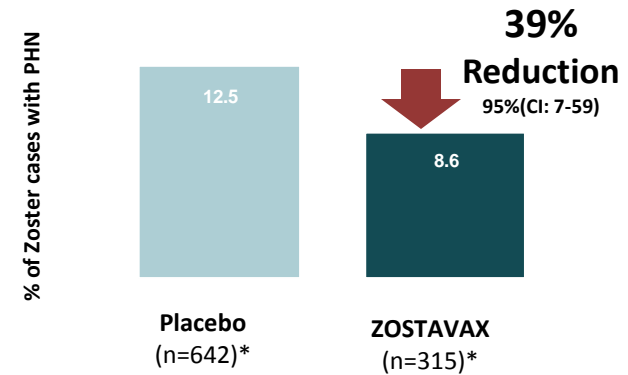
Overall Incidence of Herpes Zoster (HZ) In patients 50-59 y.o.¹



Overall Incidence of Herpes Zoster (HZ) In patients ≥60 y.o.²



Overall % of Zoster cases with Postherpetic Neuralgia (PHN) In patients who develop HZ postvaccination ≥60 y.o.



* Number of Herpes zoster cases

ZOSTAVAX has demonstrated a favorable safety profile

- The incidence of serious adverse events (SAEs) was comparable to placebo
- The most common adverse event is injection site reactions

ZOSTAVAX has demonstrated

- a significantly higher varicella-zoster virus gpELISA antibody GMT at 6 weeks post-vaccination compared with placebo

Injection-Site and Systemic Adverse Experiences

Reported by vaccine report card in $\geq 1\%$ of adults who received ZOSTAVAX or placebo (0 to 42 days postvaccination) in the AE monitoring substudy of the Shingles Prevention Study

Adverse Experience	ZOSTAVAX® [Zoster Vaccine Live (Oka/Merck)] (n = 3,345) %	Placebo (n= 3,271) %
<i>Injection Site</i>		
Erythema*	33.7	6.4
Pain/tenderness*	33.4	8.3
Swelling*	24.9	4.3
Hematoma	1.4	1.4
Pruritus	6.6	1.0
Warmth	1.5	0.3
<i>Systemic</i>		
Headache	1.4	0.8

*Designates a solicited adverse experience. Injection-site adverse experiences were solicited only from Days 0–4 postvaccination.

Prevention Summary

Prevention is possible

Age 50 and older

Immunocompetent

Future to bring killed vaccine

Immunocompromised

How to Improve Vaccination Rates



- Know the rules
- Establish protocols/standing orders
- Make strong recommendations
- If your office cannot vaccinate, refer
- Partner with pharmacists and pharmacies
- Partner with public health vaccinators
- Be captain of the immunization ship!

Know The Rules:

2015 ACIP Adult Immunization Schedule

Recommended Adult Immunization Schedule—United States - 2015

Note: These recommendations must be read with the footnotes that follow containing number of doses, intervals between doses, and other important information.

Figure 1. Recommended adult immunization schedule, by vaccine and age group¹

VACCINE ▼	AGE GROUP ►	19-21 years	22-26 years	27-49 years	50-59 years	60-64 years	≥ 65 years
Influenza ^{*2}		1 dose annually					
Tetanus, diphtheria, pertussis (Td/Tdap) ^{*3}		Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 yrs					
Varicella ^{*4}		2 doses					
Human papillomavirus (HPV) Female ^{*5}		3 doses					
Human papillomavirus (HPV) Male ^{*5}		3 doses					
Zoster ⁶					Begin?	1 dose	
Measles, mumps, rubella (MMR) ^{*7}		1 or 2 doses					
Pneumococcal 13-valent conjugate (PCV13) ^{*8}		1-time dose					
Pneumococcal polysaccharide (PPSV23) ⁸		1 or 2 doses					1 dose
Meningococcal ^{*9}		1 or more doses					
Hepatitis A ^{*10}		2 doses					
Hepatitis B ^{*11}		3 doses					
<i>Haemophilus influenzae</i> type b (Hib) ^{*12}		1 or 3 doses					

*Covered by the Vaccine Injury Compensation Program

CDC Advisory Cmte. on Immunization Practices.

<http://www.cdc.gov/vaccines/schedules/downloads/adult/adult-schedule.pdf>

Accessed February 15, 2015.

Take an aggressive approach!

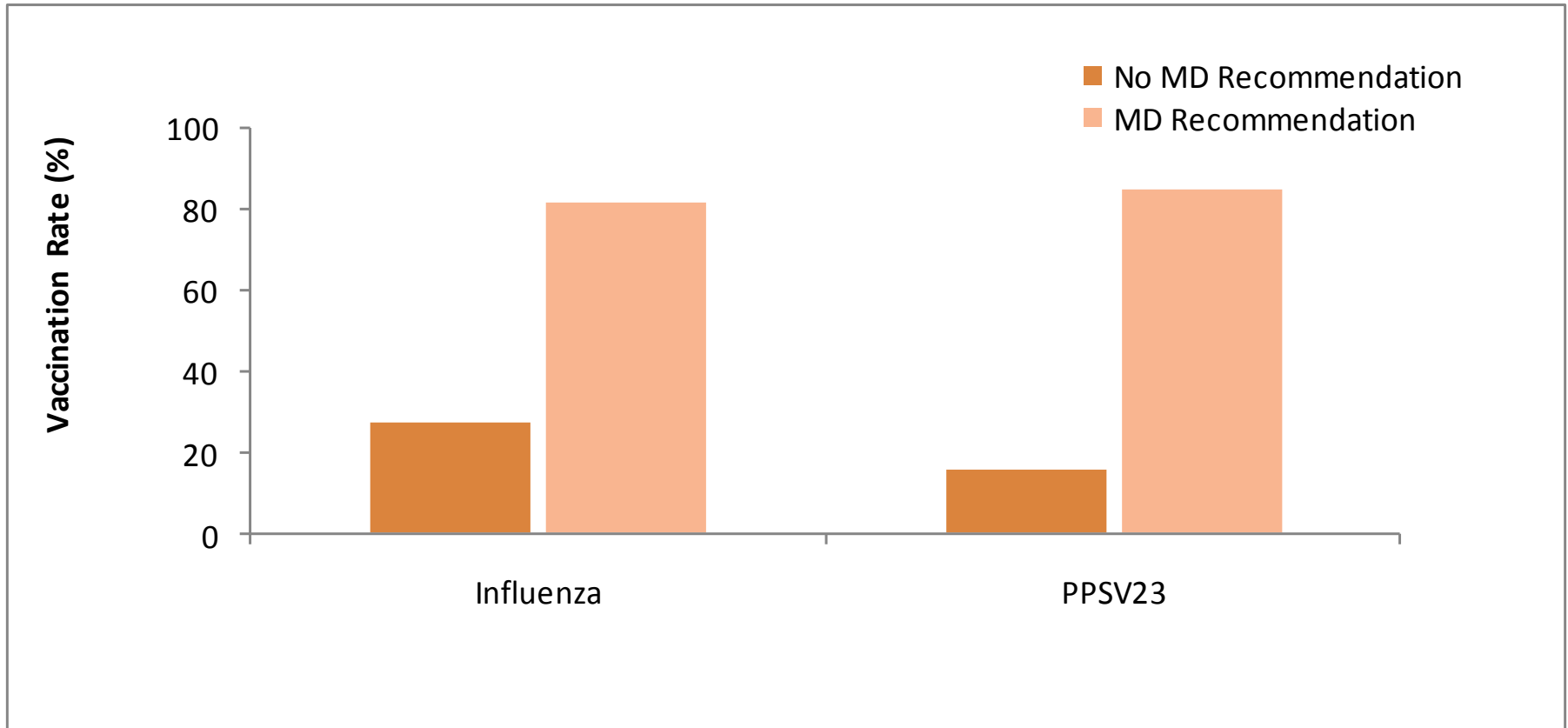
- Your recommendation is key
 - 88% of consumers said they were likely to get vaccinated if recommended by their doctor*
- Standing orders are one of the most effective ways to increase vaccination
- Utilize EMR to your advantage
 - Use automatic reminders
 - Some can run the daily patient list for immunizations that are due; have staff administer on arrival
 - Use patient portal

Protocols/Standing Orders

- Delegate! Get your staff involved
 - Have them ask about vaccination status when doing vital signs or medication reconciliation
 - They can provide vaccine information to patient
 - Establish standing orders for automatic administration of all vaccines, not just flu
- Appoint an office champion to spearhead patient identification and vaccination efforts
- Free download of standing order forms at www.immunize.org/standing-orders

Provider Recommendation Can Overcome Negative Attitude Among Patients

Vaccination Rates Among High Risk Patients With Negative Attitudes



MD, medical doctor.

Nichol KL, et al. J Gen Intern Med.
1996;11(11):673-677.

If Your Office Cannot Vaccinate, Refer



- Know the rules.
- In Missouri, pharmacists can only provide vaccinations recommended by the ACIP
 - HZ vaccine after age 60
 - They have more hours of service than MD offices
 - Primary reason for referral may be Medicare Part D
 - Up to age 65 using private insurance—in office?
 - Can they vaccinate below that age with prescription?
- What are the rules for public health vaccinators?

Barriers

- “But I’m too busy”
 - What makes immunizing your patient less important than other disease issues or giving therapy for other conditions?
- *“It’s too costly to stock all these vaccines”*
- *“But its frozen”*
- *“But it has to be reconstituted”*
- *“But it expires in 60 minutes”*

Barriers

- Reimbursement for adult vaccines better than for pediatric ones
- Can bill \$30-\$96 above vaccine cost *in addition to* vaccine administration cost per vaccine
- Many companies will provide vaccines up to 90 days before payment is due—can bill for them by then!!
- Most companies will buy back outdated/damaged product or freezer failures

Not
How important is it to me?
But
How important is it for patients?
And
How can I make it happen?